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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,883	01/23/2004	Michael Hensel	ICI 104 DIV	8282

23579 7590 06/28/2007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
06/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,883	HENSEL ET AL.	
	Examiner	Art Unit	
	Khatol S. Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,22-49,68-70 and 91-98* is/are pending in the application.

4a) Of the above claim(s) *1-16,30-34,41,42,69,70 and 91-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29,35-40 and 43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/2004 and 10/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to restriction of 04/02/2007 is acknowledged.

Status of Claims

2. Claims 1-16, 22-49, 68-70, and 91-98 are pending. Claims 17-21, 50-68, 71-90 and 99-100 have been canceled by previous amendments.

Priority

3. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. Applicants' amendment to the specification of 01/23/2004 has been noted but it is not complete. The amendment recited that "This application is a divisional of U.S.S.N. 09/763,620 filed March 2, 2001 entitled "Attenuated Salmonella SPI2 Mutants as Antigen Carriers", which is a filing under 35 USC § 371 of PCT/EP99/06514 (WO 00/14240) filed on September 3, 1999, which claims priority to European Patent Application No. 98116827.1 filed September 4, 1998. The status of application 09/763,620 filed March 2, 2001 needs to be updated which is now US Patent # 6,936,425 issued August 30, 2005.

Specification

4. The disclosure is objected to because of the following informalities:

The use of the trademarks such as Taqplus, Stratagene, FACScan, MiniMACS etc have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks

Abbreviation such as "LB" medium has been noted in the specification. The full name of such abbreviations are required when they appear first time in the specification.

Multiple blank spaces have been noticed in the specification. It is not clear if these spaces are purposely left blank or some text is missing from the specification.

There are reference numbers on the upper left hand side and lower right side on all pages of the specification, which needs to be removed.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate corrections are required.

Information Disclosure Statement

5. The information disclosure statement filed 1/23/2004 and 10/18/2006 have been considered. Initialed copies are enclosed. However, the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A (1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Election/Restrictions

6. Applicants' election with traverse of 4/02/2007 is acknowledged. Applicants elected group III claims 22-49 and 69-70, which are drawn to attenuated bacterial cells. For election of species applicants elected *Salmonella* species and sse genes. The traversal is on the ground(s) that Claims 1-16, 22-49, 69-70 and93-98 Should be Rejoined Because They Share Unity of Invention. The above-referenced application is a divisional application of a national phase filing under 35 U.S.C. § 371. Therefore, PCT Rules Rule 13.1 and 13.2 must be applied instead of U.S. restriction practice. 37 C.F.R.

§ 1.499; see also MPEP § 1893.03(d). Applicants respectfully submit that the Examiner has incorrectly restricted the pending claims by applying U.S. restriction practice rather than the unity of invention standard.

This is not found persuasive because this application is a divisional application which is filed under 35 U.S.C. 111 (a) and the parent application was filed under 35 U.S.C. 371. 37 C.F.R. § 1.499 and MPEP § 1893.03(d) refer to unity of invention during the national stage application. This application is a divisional of a national stage application. Therefore, U.S. restriction practice has been applied. Even if lack of unity as applicants argued was applied as set before in the parent application # 09/763,620 the inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature linking group I -IV appears to be products and genes of the SPI2 locus (Salmonella pathogenicity Island 2). However, Hensel et al. (Molecular Microbiology Vol. 24 (1) pp. 155-167, 1997, prior art of record) teach products and genes of the SPI2 locus (Salmonella pathogenicity Island 2)(see summary and title). Therefore, the technical feature linking the inventions of groups I- IV does not constitute a special technical feature as defined by the PCT Rule 13.2, as it does not define a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-16, 30-34, 41-42, 69-70 and 91-98 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions.

Claims 22-29, 35-40 and 43-49 are under consideration.

Double Patenting

7. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

8. Claims 22-29, 35-40 and 43-49 of this application conflict with claims 22-29, 35-40 and 43-49 of Application No.10/007,463. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicants are required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 22-29, 35-40 and 43-49 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 22-29, 35-40 and 43-49 are directed to microorganisms (attenuated gram-negative cell), which have the same characteristics and utility as microorganisms found naturally and therefore does not constitute as patentable subject matter. It is noted that the claims recite that the microorganisms have been attenuated or have mutations, however mutations occur in nature and therefore does not exclude products of nature. In the absence of the hand of man, naturally occurring products are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Mere purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also

American Wood v. Fiber Disinter, gratin, g Co., 90 US 566 (1974); American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment to the claims to recite the essential purity of the claimed products is suggested to obviate this rejection. For example, "An isolated attenuated gram –negative cell..."

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention appears to employ novel strains of *Salmonella* serotype typhimurium Definitive Type 104 (DT 104). It is not clear if the written description is sufficiently repeatable to avoid the need for a deposit. Further it is unclear if the starting materials were readily available to the public at the time of invention.

It does not appear that a deposit was made in this application. It is not also clear if the deposit meet all the criteria set forth in 37 CFR 1.801-1.809. Because it is not clear that *Salmonella* serotype typhimurium having the accession numbers of Definitive Type 104 (DT 104) are known and publicly available or can be reproducibly isolated from nature without undue experimentation. Without a publicly available deposit of the above strains, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the strains is an unpredictable event.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record that has the authority and control over the conditions of deposit over his or her signature and registration number.

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the repository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;

2) The name and address of the depositor;

3) The date of deposit;

4) The identity of the deposit and the accession number given by the depository;

5) The date of the viability test;

6) The procedures used to obtain a sample if test is not done by the depository; and

7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the strains described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d.1216, 227 USPQ (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

13. Claims 22-29, 35-40 and 43-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

Claim 22 recites, an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. The claim broadly recite any gram-negative cell, any mutation and any SPI2 locus.

The specification teaches that a recent study revealed that the inactivation of individual *Salmonella* genes causing attenuation of virulence directly influences the quality of an immune response against the vaccine carrier strain. From this finding, one can conclude that it might be possible to generate a variety of differently attenuated *Salmonella* vaccine strains (see page 4, lines 14-16) Thus, in a further aspect, the present invention is an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. Genes present in the *Salmonella* pathogenicity island 2 that encode for a variety of proteins involved in type III secretion and those that are required for systemic spread and survival within phagocytic cells are ideal candidates for attenuation of pathogenic *Salmonella* ssp. (see page 11,lines 9-17)

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Since the disclosure fails to

describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "any gram negative cell, any mutation in any locus of SPI2 " alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

The closest prior art Deiwick et al. (Journal of Bacteriology, Vol. 180, No.18, pp. 4775-4780, September 1, 1998) teach that the *Salmonella typhimurium* genome contains two pathogenicity islands (SPI) with genes encoding type III secretion systems or virulence proteins (see abstract). The prior art teach some mutations in SPI2 and SPI1 genes but not "any gram negative cell, any mutation in any locus of SPI2". Substitution of amino acids into a known sequence as well as identifying and using fragments of proteins containing an isolated functional domain of a protein is within the realm of protein chemistry and is one of the most unpredictable areas of protein chemistry. The art for example Burgess et al. (J of Cell Biology, 1990 Vol. 111, pp.2129-2138) teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Furthermore, Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp. 1247-1252) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The protein itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016. Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 111, clearly states that "applicant must convey with reasonable clarity to those

skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Applicants are reminded that Vas-Cath make clear that the written description provision of 35 USC 112 is severable from its enablement provision. Furthermore, in The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 22, 24, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Hensel et al. (Journal of Bacteriology, Vol. 179, No. 4, pp. 1105-1111, February 1997). Prior art of record, applicants' 1449.

Claims are drawn to an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell.

Hensel et al. teach an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. (see abstract and page 1105 right column 1st full paragraph). Hensel et al. teach enterobactericae and *Salmonella* cell (see bacterial strains, page 1105 and table 1, page 1106. Hensel et al. teach broad host range for *Salmonella* species causing disease (see page 1105). The prior teach the claimed invention.

16. Claims 22, 24, 25, 26, 35, 38, 39, 40, 44, 45, 46, 47, 48 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Shea et al. (Proc. Natl. Acad. Sci. USA Vol. 93, pp. 2503-2597, March 1996). Prior art of record, applicants' 1449.

Claims are drawn to an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell.

Shea et al. teach an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. (see abstract and page 2593). Shea et al. teach enterobactericae and Salmonella cell (see bacterial strains, page 2593 and figure 1, page 2594). Shea et al. et al. teach broad host range for *Salmonella* species causing disease (see page 2593). Shea et al. teach insertion mutation and insertion cassettes (see pages 2593, 2594 and fig 1). Shea et al. teach antibiotic resistance (see 2594 under results). Shea et al. teach a gene outside of SPI2 locus (see page 2595 under mapping boundaries of

SPI2). Shea et al. do not explicitly teach invertase and transactivator cassettes, however these cassettes would be inherent in insertion cassettes taught by Shea et al. (see pages 2593, 2594 and fig 1). The prior teach the claimed invention.

17. Claims 22, 23, 24, 25, 26, 28, 29, 35, 37, 38, 39, 40, 44, 45, 46, and 49 are rejected under 35 U.S.C. 102(a) as being anticipated by Deiwick et al. (Journal of Bacteriology, Vol. 180, No.18, pp. 4775-4780, September 1, 1998).

Claims are drawn to an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell.

Deiwick et al. teach an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. (see abstract and page 4776). Deiwick et al. teach enterobactericae and *Salmonella typhimurium cell* (see bacterial strains, page 4775). Deiwick et al.. teach broad host range for *Salmonella* species causing disease (see page 4775). Deiwick et al. teach insertion mutation and insertion cassettes (see pages 4776 –4777 and fig 1). Deiwick et al. teach deletion mutations too (see page 4779 lack of SPI2 components). Deiwick et al. teach antibiotic resistance (see 4778). Deiwick et al. teach a gene outside of SPI2 locus (see page 4779). Deiwick et al. teach non-polar mutations (see page 4778). Deiwick et al. teach sse gene (see page 4775, left column). The prior teach the claimed invention.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 22, 40 and 43 are rejected under 35 U.S.C. 103(a) as being anticipated by Deiwick et al. (Journal of Bacteriology, Vol. 180, No.18, pp. 4775-4780, September 1, 1998) in view of Tsolis et al. (Infection and Immunity Vol. 63, No. 5, pp. 1739-1744, May 1995).

Claims 22 and 40 drawn to an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. Claim 43 further recite an additional gene superoxide dismutase.

The teachings of Deiwick et al. have been recited above. Deiwick et al. do not specifically teach an additional superoxide dismutase gene.

Tsolis et al. teach superoxide dismutase genes (sodA and sodB) of *Salmonella typhimurium* (see abstract and pages 1741- 1743). Tsolis et al. also teach attenuated *Salmonella typhimurium* (see page 1743). Tsolis et al. also teach the role of superoxide dismutase genes (sodA and sodB) in protection of bacteria from oxidative killing (see page 1739).

It would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to combine the teachings of Deiwick et al., an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated with the teachings of Tsolis et al. superoxide dismutase genes (sodA and sodB) of *Salmonella typhimurium* to obtain an attenuated gram-negative cell comprising the SPI2 gene locus, wherein at least one gene of the SPI2 locus is inactivated, wherein said inactivation results in an attenuation/reduction of virulence compared to the wild type of said cell. One of skilled in the art would have been motivated by the teaching of Deiwick et al. that mutations in SpI2 lead to strong reduction of virulence and certain mutations in SpI2 affect the ability of *Salmonella typhimurium* to secret SPI1 effector proteins (see abstract). One of skilled in the art would have also been motivated by the teaching of Deiwick et al. that mutations in SPI2

affect the expression of SPI1 genes. Furthermore, mutations in SPI2 results in an altered resistance of Salmonella *typhimurium* to various antibiotics (see Deiwick et al. page 4775 right column second paragraph).

Status of the Claims

20. Claims 22-29, 35-40 and 43-49 are rejected.

Claims 1-16, 30-34, 41-42, 69-70 and 91-98 are withdrawn from consideration as being drawn to a nonelected inventions.

Claims 27 and 36 are free of prior art. Claim 27 is drawn to a *Salmonella* serotype *typhimurium* Definitive Type 104 (DT 104) cell and claim 36 to a deletion comprising at least 6 nucleotides. The closest prior art Deiwick et al. (Journal of Bacteriology, Vol. 180, No.18, pp. 4775-4780, September 1, 1998) does not teach or suggest the specific strain *Salmonella* serotype *typhimurium* Definitive Type 104 (DT 104) or deletion of at least 6 nucleotides.

Conclusion

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is 571-272-0863. The examiner can normally be reached on Monday-Friday 7:30 AM-5:00 PM If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached on 571-272-0787

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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